



General

Guideline Title

Tocolysis for women in preterm labour.

Bibliographic Source(s)

Royal College of Obstetricians and Gynaecologists (RCOG). Tocolysis for women in preterm labour. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2011 Feb. 13 p. (Green-top guideline; no. 1b). [38 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

In addition to these evidence-based recommendations, the guideline development group also identifies points of best clinical practice in the original guideline document.

Classification of evidence levels (1++ to 4) and grades of recommendations (A–D) are defined at the end of the "Major Recommendations" field.

Uses of Tocolysis for Women in Preterm Labour

Does Tocolysis Prevent Preterm Birth?

A - There is no clear evidence that tocolytic drugs improve outcome and therefore it is reasonable not to use them. However, tocolysis should be considered if the few days gained would be put to good use, such as completing a course of corticosteroids or in utero transfer.

Does the Use of Any Tocolytic Drug Prevent Perinatal or Neonatal Death and Neonatal Morbidity?

A - Use of a tocolytic drug is not associated with a clear reduction in perinatal or neonatal mortality, or neonatal morbidity.

When Should Tocolytic Drugs Be Used?

B - Tocolysis may be considered for women with suspected preterm labour who have had an otherwise uncomplicated pregnancy. It is reasonable not to use any tocolytic drug.

Is One Tocolytic Drug More Effective in Preventing Preterm Birth Than Another?

A - Nifedipine and atosiban have comparable effectiveness in delaying birth for up to seven days.

A - Compared with beta-agonists, nifedipine is associated with improvement in neonatal outcome, although there are no long-term data.

What Are the Comparative Adverse Effects for the Woman of Alternative Tocolytic Drugs for Preterm Labour?

A - Beta-agonists have a high frequency of adverse effects. Nifedipine, atosiban and the cyclo-oxygenase (COX) inhibitors have fewer types of adverse effects, and they occur less frequently than for beta-agonists but how they compare with each other is unclear.

B - Using multiple tocolytic drugs appears to be associated with a higher risk of adverse effects and so should be avoided.

What Are the Comparative Effects for the Baby of Alternative Tocolytic Drugs for Preterm Labour?

B - The comparative effects for the baby of alternative drugs are unclear. Most drugs have been compared with beta-agonists. There are insufficient data on long-term follow-up for reliable conclusions about the effects on the baby for any of these tocolytic drugs.

Is Maintenance Tocolytic Therapy Worthwhile?

A - There is insufficient evidence for any firm conclusions about whether or not maintenance tocolytic therapy following threatened preterm labour is worthwhile. Thus, maintenance therapy is not recommended.

Summary

Use of a tocolytic drug is not associated with a clear reduction in perinatal or neonatal mortality or neonatal morbidity. The main effect of tocolytic drugs when used for women in preterm labour is to reduce the numbers who deliver within 48 hours or within 7 days of commencing the drug. Data on long-term outcome are sparse. It remains plausible that, for selected women, such as those who require transfer for neonatal care or time to complete a course of corticosteroids, there may be benefit associated with tocolysis. However, this benefit has not been formally evaluated in randomised trials.

If reliable prediction of which women in suspected preterm labour are likely to have a preterm birth were possible, the use of tocolysis could be reserved for these women. Unfortunately, few tests offer useful predictive value. Fetal fibronectin has been advocated as a promising predictive test but it may have limited accuracy in predicting preterm birth within 7 days for women with symptoms of preterm labour. Ultrasound assessment of cervical length is also a promising predictive test for symptomatic women. It remains unclear whether any predictive test, or combination of tests, is sufficiently accurate to be cost effective.

If the decision is made to use a tocolytic drug, nifedipine and atosiban appear to have comparable effectiveness in delaying delivery, with fewer maternal adverse effects and less risk of rare serious adverse events than alternatives such as ritodrine or indomethacin. There is limited evidence that use of nifedipine, rather than a beta-agonist, is associated with improved short-term neonatal outcome. There is little information about the long-term growth and development of the child for any of the drugs.

Ritodrine and atosiban are licensed in the UK for the treatment of threatened preterm labour. Although the use of nifedipine for preterm labour is an unlicensed indication, it has the advantages of oral administration and a low purchase price.

The available evidence should be discussed with the woman and her partner and their preferences taken into account in determining her care.

Definitions:

Grades of Recommendation

A - At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; *or*

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results

B - A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results;
or

Extrapolated evidence from studies rated as 1++ or 1+

C - A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results;
or

Extrapolated evidence from studies rated as 2++

D - Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Classification of Evidence Levels

1++ High-quality meta-analyses, systematic review of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1- Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2- Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g., case reports, case series

4 Expert opinion

Good Practice Point - Recommended best practice based on the clinical experience of the guideline development group

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Preterm labour

Note: Tocolysis has been advocated for the management of intrapartum fetal distress and impaired fetal growth and to facilitate external cephalic version at term. These uses are not considered in this guideline. Also outside the scope of this guideline are interventions aimed at preventing the onset of preterm labour, for women at risk of preterm birth, and interventions to improve outcome for children at risk of being born preterm, such as use of antenatal corticosteroids and of magnesium sulphate for neuroprotection.

Guideline Category

Treatment

Clinical Specialty

Family Practice

Obstetrics and Gynecology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To summarise evidence about the effectiveness and safety of tocolytic drugs for treatment of preterm labour and provide guidance on incorporating this evidence into clinical practice

Target Population

Women in preterm labor

Interventions and Practices Considered

Tocolytic drugs including:

- Atosiban
- Nifedipine
- Ritodrine
- Magnesium sulphate (considered but not recommended for tocolysis)
- Indomethacin
- Beta-agonists
- Nitroglycerine (considered but no recommendation made)

Note: Use of tocolytic therapy in multiple pregnancies and maintenance tocolytic therapy were considered but not recommended.

Major Outcomes Considered

- Prolongation of pregnancy
- Preterm birth rates
- Perinatal or neonatal morbidity
- Adverse effects of tocolytic drugs

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

This Royal College of Obstetricians and Gynaecologists (RCOG) guideline was developed in accordance with the standard methodology for producing RCOG Green-top guidelines (see "Availability of Companion Documents" field). The Cochrane library (including the Database of Systematic Reviews and the Cochrane Control Register of Controlled Trials), the Database of Abstracts of Reviews and Effects, EMBASE, American College of Physicians (ACP) Journal Club and Medline, including in-process and other non-indexed citations, were searched from 2000 to September 2010 to identify all relevant randomised controlled trials (RCTs), systematic reviews and meta-analyses published since the previous edition of the guideline. The databases were searched using the relevant MeSH terms including all sub-headings. Search terms included were: 'preterm labour', 'preterm birth', 'tocolysis', 'tocolytic', 'beta-agonist', 'calcium channel blocker', 'magnesium sulphate', 'nitric oxide donor', 'oxytocin

receptor antagonist', 'prostaglandin synthetase inhibitor', 'magnesium sulphate' and 'uterine contraction + suppression'. The search was limited to humans and the English language. The National Library for Health and the National Guideline Clearinghouse were also searched for relevant guidelines and reviews.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence Levels

- 1++ High-quality meta-analyses, systematic review of randomised controlled trials or randomised controlled trials with a very low risk of bias
- 1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
- 1- Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
- 2++ High-quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
- 2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
- 2- Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
- 3 Non-analytical studies, e.g., case reports, case series
- 4 Expert opinion

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Reviewing and Grading of Evidence

Once the evidence has been collated for each clinical question it needs to be appraised and reviewed (refer to section 3 in "Development of RCOG Green-top guidelines: producing a clinical practice guideline" for information on the formulation of the clinical questions; see the "Availability of Companion Documents" field). For each question, the study type with least chance of bias should be used. If available, randomised controlled trials (RCTs) of suitable size and quality should be used in preference to observational data. This may vary depending on the outcome being examined.

The level of evidence and the grade of the recommendations used in this guideline originate from the guidance by the Scottish Intercollegiate Guidelines Network (SIGN) Grading Review Group, which incorporates formal assessment of the methodological quality, quantity, consistency, and applicability of the evidence base. The methods used to appraise individual study types are available from the SIGN Web site (www.sign.ac.uk/methodology/checklists.html). An objective appraisal of study quality is essential, but paired reviewing by guideline leads may be impractical because of resource constraints.

Once evidence has been collated and appraised, it can be graded. A judgement on the quality of the evidence will be necessary using the grading system (see the "Rating Scheme for the Strength of the Evidence" field). Where evidence is felt to warrant 'down-grading', for whatever reason, the rationale must be stated. Evidence judged to be of poor quality can be excluded. Any study with a high chance of bias (either 1– or 2–) will be excluded from the guideline and recommendations will not be based on this evidence. This prevents recommendations being based on poor-quality RCTs when higher-quality observational evidence is available.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Development

The development of guidelines involves more than the collation and reviewing of evidence. Even with high-quality data from systematic reviews of randomised controlled trials, a value judgement is needed when comparing one therapy with another. This will therefore introduce the need for consensus.

Royal College of Obstetricians and Gynaecologists (RCOG) Green-top guidelines are drafted by nominated developers, in contrast to other guideline groups such as the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN), who use larger guideline development groups. Equally, in contrast to other guideline groups, the topics chosen for development as Green-top guidelines are concise enough to allow development by a smaller group of individuals.

In agreeing the precise wording of evidence-based guideline recommendations and in developing consensus-based 'good practice points', the Guidelines Committee (GC) will employ an informal consensus approach through group discussion. In line with current methodologies, the entire development process will follow strict guidance and be both transparent and robust. The RCOG acknowledges that formal consensus methods have been described but these require further evaluation in the context of clinical guideline development. It is envisaged that this will not detract from the rigor of the process but prevent undue delays in development.

Rating Scheme for the Strength of the Recommendations

Grades of Recommendation

A - At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; *or*

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results

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Extrapolated evidence from studies rated as 1++ or 1+

C - A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results;
or

Extrapolated evidence from studies rated as 2++

D - Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Good Practice Point: Recommended best practice based on the clinical experience of the guideline development group

Cost Analysis

A cost decision analysis in the USA comparing terbutaline, magnesium sulphate, indomethacin and nifedipine concluded that indomethacin and nifedipine were the least expensive options. A similar analysis in Germany compared atosiban with beta-agonists and concluded atosiban was the cheaper option. The relevant comparison for the UK would be of atosiban with nifedipine.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Following discussion in the Guidelines Committee (GC), each Green-top guideline is formally peer reviewed. At the same time, the draft guideline is published on the Royal College of Obstetricians and Gynaecologists (RCOG) Web site for further peer discussion before final publication.

All comments will be collated by the RCOG and tabulated for consideration by the guideline leads. Each comment will require discussion. Where comments are rejected then justification will need to be made. Following this review, the document will be updated and the GC will then review the revised draft and the table of comments.

Once the GC signs-off on the guideline, it is submitted to the Standards Board for approval before final publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate and safe use of tocolytic drugs for treatment of preterm labor
- Women most likely to benefit from use of a tocolytic drug are those who are in very preterm labour, those needing transfer to a hospital which can provide neonatal intensive care and those who have not yet completed a full course of corticosteroids.

Potential Harms

General

There may be direct or indirect adverse effects of tocolytic drugs (including prolongation of pregnancy when this is detrimental to the baby), which counteract their potential gain.

Beta-Agonists

Common adverse effects when beta-agonists are compared with placebo include palpitations (38% for beta-agonists compared with 4% for placebo), tremor (39% compared with 4%), nausea or vomiting (21% compared with 12%), headache (19% compared with 5%), chest pain (10% compared with 1%) and dyspnoea (14% compared with 3%). Women allocated beta-agonists were far more likely to stop treatment because of adverse effects than those allocated placebo (five trials, 1081 women; relative risk [RR] 11.38; 95% confidence interval [CI] 5.21–24.86). Rare but serious and potentially life-threatening adverse effects have been reported following beta-agonist use and there are case reports

of a small number of maternal deaths associated with use of these drugs. Pulmonary oedema is a well-documented complication, usually associated with aggressive intravenous hydration. A systematic review reported one case of pulmonary oedema among 852 women (1/425 beta-agonists compared with 0/427 placebo).

Calcium Channel Blockers

No trials have compared calcium channel blockers with placebo for treatment of preterm labour. When compared with other tocolytic drugs (ritodrine in most of the trials), calcium channel blockers are associated with fewer adverse effects (RR 0.32; 95% CI 0.24–0.41) and less need to stop treatment because of adverse effects (RR 0.14; 95% CI 0.05–0.36). Reported adverse effects for nifedipine, the most widely used calcium antagonist, include flushing, palpitations, nausea and vomiting and hypotension. Nifedipine is contraindicated if the woman has cardiac disease and should be used with caution if she has diabetes or multiple pregnancy, owing to the risk of pulmonary oedema. Total dose of nifedipine above 60 mg appears to be associated with a three- to four-fold increase in adverse events such as headache and hypotension.

Atosiban

With atosiban, reported adverse effects are nausea (11% for atosiban compared with 5% for placebo), vomiting (3% compared with 4%), headache (5% compared with 7%), chest pain (1% compared with 4%) and dyspnoea (0.4% compared with 3%). Only nausea was statistically significantly increased (OR 2.28, 95% CI 1.26–4.13). Women allocated atosiban were also more likely to stop treatment because of adverse effects than those allocated placebo (two trials, 613 women; RR 4.02; 95% CI 2.05–7.85). A common reason for stopping treatment was injection-site reactions. Compared with beta-agonists, however, fewer women allocated atosiban stop treatment because of adverse effects (RR 0.04; 95% CI 0.02–0.11; number needed to treat 6; 95% CI 5–7). Atosiban has not been compared with calcium antagonists in randomised trials. Diabetes and cardiac disease are not contraindications to atosiban.

Contraindications

Contraindications

- Any contraindication to prolonging pregnancy is a contraindication to tocolytic therapy; for example, known lethal congenital or chromosomal malformation, intrauterine infection, severe pre-eclampsia, placental abruption, advanced cervical dilatation and evidence of fetal compromise or placental insufficiency. Relative contraindications include mild haemorrhage due to placenta praevia, nonreassuring cardiotocograph, fetal growth restriction and multiple pregnancy.
- Nifedipine is contraindicated if the woman has cardiac disease and should be used with caution if she has diabetes or multiple pregnancy, owing to the risk of pulmonary oedema.
- Using more than one type of tocolytic in combination with another appears to increase the risk of adverse effects and so should be avoided.

Qualifying Statements

Qualifying Statements

- The Royal College of Obstetricians and Gynaecologists (RCOG) produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.
- This means that RCOG guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

Implementation of the Guideline

Description of Implementation Strategy

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Audit Criteria/Indicators

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Royal College of Obstetricians and Gynaecologists (RCOG). Tocolysis for women in preterm labour. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2011 Feb. 13 p. (Green-top guideline; no. 1b). [38 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Feb

Guideline Developer(s)

Royal College of Obstetricians and Gynaecologists - Medical Specialty Society

Source(s) of Funding

Royal College of Obstetricians and Gynaecologists

Guideline Committee

Guidelines Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Guideline authors are required to complete a "declaration of interests" form.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the [Royal College of Obstetricians and Gynaecologists \(RCOG\) Web site](#) .

Availability of Companion Documents

The following are available:

- Development of RCOG Green-top guidelines: policies and processes. Clinical Governance Advice No 1a. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 6 p. Electronic copies: Available from the [Royal College of Obstetricians and Gynaecologists \(RCOG\) Web site](#) .
- Development of RCOG Green-top guidelines: producing a scope. Clinical Governance Advice No 1b. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 4 p. Electronic copies: Available from the [RCOG Web site](#) .
- Development of RCOG Green-top guidelines: producing a clinical practice guideline. Clinical Governance Advice No 1c. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 13 p. Electronic copies: Available from the [RCOG Web site](#) .
- Development of RCOG Green-top guidelines: consensus methods for adaptation of Green-top guidelines. Clinical Governance Advice No 1d. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2010 Feb. 9 p. Electronic copies: Available from the [RCOG Web site](#) .

In addition, auditable standards can be found in section 14 of the [original guideline document](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on June 10, 2011. The information was verified by the guideline developer on July 22, 2011. This summary was updated by ECRI Institute on September 18, 2015 following the U.S. Food and Drug Administration advisory on non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs).

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